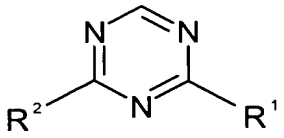
Claims

What is claimed is:

1. A compound having the formula:



wherein,

Each R^1 and R^2 is independently R^3; R^8; NHR^3; NHR^5; NHR^6; NR^5R^5; NR^5R^6; SR^5; SR^6; SR^3; OR^5; OR^6; OR^3; $C(O)R^3$; heterocyclyl optionally substituted with 1-4 independent R^4 on each ring; or C1-C10 alkyl substituted with 1-4 independent R^4;

Each R^3 is independently aryl; phenyl optionally substituted with 1-5 independent R^4 on each ring; or heteroaryl optionally substituted with 1-4 independent R^4 on each ring;

Each n is independently 1 or 2;

Each m is independently 0, 1, 2, 3, or 4;

Each R^4 is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^8; halo; haloalkyl; CF_3; SR^5; OR^5; $OC(O)R^5$; NR^5R^5; NR^5R^6; NR^5R^{16}; $COOR^5$; NO_2; CN; $C(O)R^5$; $C(O)C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nR^5$; $S(O)_nNR^5R^5$; $NR^5C(O)NR^5R^5$; $NR^5C(O)C(O)R^5$; $NR^5C(O)R^5$; $NR^5(COOR^5)$; $NR^5C(O)R^8$; $NR^5S(O)_nNR^5R^5$; $NR^5S(O)_nR^5$; $NR^5S(O)_nR^8$; $NR^5C(O)C(O)NR^5R^5$; $NR^5C(O)C(O)NR^5R^6$; $OC(O)NR^5R^5$; $OS(O)_nNR^5R^5$; $NR^5S(O)_nOR^5$; $P(O)(OR^5)_2$; C1-C10 alkyl substituted with 1-3 independent aryl, R^7 or R^8; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^8;

Each R^5 is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^9; haloalkyl; C1-C10 alkyl substituted with 1-3 independent aryl, R^7 or R^9 groups; C3-C10 cycloalkyl substituted

with 1-3 independent aryl, R^7 or R^9 groups; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^9;

Each R^6 is independently $C(O)R^5$, $COOR^5$, $C(O)NR^5R^5$, $C(N\ R^5)\ NR^5R^5$, or $S(O)_n\ R^5$;

Each R^7 is independently halo, CF_3, SR^{10}, OR^{10}, $OC(O)R^{10}$, $NR^{10}R^{10}$, $NR^{10}R^{11}$, $NR^{11}R^{11}$, $COOR^{10}$, NO_2, CN, $C(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $C(O)NR^{10}R^{10}$, $N(R^{10})C(O)R^{10}$, $N(R^{10})\ (COOR^{10})$, $S(O)_nNR^{10}R^{10}$; $NR^{10}S(O)_nNR^{10}R^{10}$; $NR^{10}S(O)_nR^{10}$; or $P(O)(OR^5)_2$;

Each R^8 is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system comprising 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2, 3 or 4 atoms of each ring may be substituted by a substituent independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^9; halo; sulfur; oxygen; CF_3; SR^5; OR^5; $OC(O)R^5$; NR^5R^5; NR^5R^6; NR^6R^6; $COOR^5$; NO_2; CN; $C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nNR^5R^5$; $NR^5C(O)NR^5R^5$; $NR^5C(O)R^9$; $NR^5S(O)_nNR^5R^5$; $NR^5S(O)_nR^9$; C1-C10 alkyl substituted with 1-3 independent R^7, R^9 or aryl; or C2-C10 alkenyl substituted with 1-3 independent R^7, R^9 or aryl;

Each R^9 is independently a 3-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system comprising 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S, which may be saturated or unsaturated, and wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; halo; sulfur; oxygen; CF_3; haloalkyl; SR^{10}; OR^{10}; $NR^{10}R^{10}$; $NR^{10}R^{11}$; $NR^{11}R^{11}$; $COOR^{10}$; NO_2; CN; $C(O)R^{10}$; $S(O)_nR^{10}$; $S(O)_nNR^{10}R^{10}$; or $C(O)NR^{10}R^{10}$;

Each R^{10} is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; haloalkyl; C1-C10 alkyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-

C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF_3, OR^{12}, SR^{12}, $NR^{12}R^{12}$, $COOR^{12}$, NO_2, CN, $C(O)R^{12}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $N(R^{12})(COOR^{12})$, $S(O)_nNR^{12}R^{12}$, or $OC(O)R^{12}$; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF_3, OR^{12}, SR^{12}, $NR^{12}R^{12}$, $COOR^{12}$, NO_2, CN, $C(O)R^{12}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $N(R^{12})(COOR^{12})$, $S(O)_nNR^{12}R^{12}$, or $OC(O)R^{12}$;

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Each R^{11} is independently $C(O)R^{10}$, $COOR^{10}$, $C(O)NR^{10}R^{10}$ or $S(O)_nR^{10}$;

Each R^{12} is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl substituted with 1-3 independent C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF_3, OR^{13}, SR^{13}, $NR^{13}R^{13}$, $COOR^{13}$, NO_2, CN, $C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $NR^{13}C(O)R^{13}$, or $OC(O)R^{13}$; or phenyl optionally substituted with 1-3 independent C1-C10 alkyl, C2-C10 alkenyl, C2-C10 alkynyl, C3-C10 cycloalkyl, C4-C10 cycloalkenyl, halo, CF_3, OR^{13}, SR^{13}, $NR^{13}R^{13}$, $COOR^{13}$, NO_2, CN, $C(O)R^{13}$, $C(O)NR^{13}R^{13}$, $NR^{13}C(O)R^{13}$, or $OC(O)R^{13}$;

Each R^{13} is independently H; C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; C1-C10 alkyl optionally substituted with halo, CF_3, OR^{14}, SR^{14}, $NR^{14}R^{14}$, $COOR^{14}$, NO_2, CN; or phenyl optionally substituted with halo, CF_3, OR^{14}, SR^{14}, $NR^{14}R^{14}$, $COOR^{14}$, NO_2, CN;

Each R^{14} is independently H; C1-C10 alkyl; C3-C10 cycloalkyl or phenyl;

Each R^{15} is independently H; CF_3; CN; $COOR^5$; or C1-C10 alkyl substituted with 1-3 independent OR^5, SR^5, or NR^5R^5;

Each R^{16} is independently H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^8; halo; haloalkyl; CF_3; $COOR^5$; $C(O)R^5$; $C(O)C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nR^5$; $S(O)_nNR^5R^5$; C1-C10 alkyl substituted with 1-3 independent aryl, R^7, R^8, or phenyl optionally substituted with substituted with 1-4 independent R^{23}; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^8;

Each R^{17} is independently NR^5R^{16}; OR^5; SR^5; or halo;

Each R^{18} is independently C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^8; halo; haloalkyl; CF_3; $COOR^5$; $C(O)R^5$; $C(O)C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nR^5$; $S(O)_nNR^5R^5$; C1-C10 alkyl substituted with 1-3 independent aryl, R^7 or R^8; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^8;

Each R^{19} is independently H or C1-C6 alkyl;

Each R^{20} is independently NR^5R^{18}; OR^5; SR^5; or halo;

Each R^{21} is independently t-butyl, 4-carboxyphenyl, 4-carbomethoxyphenyl, or furyl substituted with 1-4 independent R^4;

Each R^{22} is independently C2-C9 alkyl substituted with 1-2 independent aryl, R^7, or R^8;

Each R^{23} is independently selected from H, C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^8; halo; haloalkyl; CF_3; SR^5; OR^5; $OC(O)R^5$; NR^5R^5; NR^5R^6; $COOR^5$; NO_2; CN; $C(O)R^5$; $C(O)C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nR^5$; $S(O)_nNR^5R^5$; $NR^5C(O)NR^5R^5$; $NR^5C(O)C(O)R^5$; $NR^5C(O)R^5$; $NR^5(COOR^5)$; $NR^5C(O)R^8$; $NR^5S(O)_nNR^5R^5$; $NR^5S(O)_nR^5$; $NR^5S(O)_nR^8$; $NR^5C(O)C(O)NR^5R^5$; $NR^5C(O)C(O)NR^5R^6$; $OC(O)NR^5R^5$; $OS(O)_nNR^5R^5$; $NR^5S(O)_nOR^5$; $P(O)(OR^5)_2$; C1-C10 alkyl substituted with 1-3 independent aryl, R^7 or R^8; or C2-C10 alkenyl substituted with 1-3 independent aryl, R^7 or R^8;

Each R^{24} is independently selected from C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; aryl; R^9; halo; sulfur; oxygen; CF_3; SR^5; OR^5; $OC(O)R^5$; NR^5R^5; NR^5R^6; NR^6R^6; $COOR^5$; NO_2; CN; $C(O)R^5$; $C(O)NR^5R^5$; $S(O)_nNR^5R^5$; $NR^5C(O)NR^5R^5$; $NR^5C(O)R^9$; $NR^5S(O)_nNR^5R^5$; $NR^5S(O)_nR^9$; C1-C10 alkyl substituted with 1-3 independent R^7, R^9 or aryl; or C2-C10 alkenyl substituted with 1-3 independent R^7, R^9 or aryl;

Each X is independently O or S;

Each V, W, Y, and Z is independently N or CR^4;

Each haloalkyl is independently a C1-C10 alkyl substituted with one or more halogen atoms, selected from F, Cl, Br, or I, wherein the number of halogen atoms may not exceed that number that results in a perhaloalkyl group;

Each aryl is independently a 6-carbon monocyclic, 10-carbon bicyclic or 14-carbon tricyclic aromatic ring system optionally substituted with 1-3 independent C1-C10 alkyl; C2-C10 alkenyl; C2-C10 alkynyl; C3-C10 cycloalkyl; C4-C10 cycloalkenyl; R^9; halo; haloalkyl; CF_3; OR^{10}; SR^{10}; $NR^{10}R^{10}$; $NR^{10}R^{11}$; $COOR^{10}$; NO_2; CN; $C(O)R^{10}$; $C(O)C(O)R^{10}$; $C(O)NR^{10}R^{10}$; $N(R^{10})C(O)NR^{10}R^{10}$; $N(R^{10})C(O)R^{10}$; $N(R^{10})S(O)_nR^{10}$; $N(R^{10})(COOR^{10})$; $NR^{10}C(O)C(O)R^{10}$; $NR^{10}C(O)R^9$; $NR^{10}S(O)_nNR^{10}R^{10}$; $NR^{10}S(O)_nR^9$; $NR^{12}C(O)C(O)NR^{12}R^{12}$; $S(O)_nR^{10}$; $S(O)_nNR^{10}R^{10}$; $OC(O)R^{10}$; C1-C10 alkyl substituted with 1-3 independent R^9, halo, CF_3, OR^{10}, SR^{10}, $OC(O)R^{10}$, $NR^{11}R^{11}$, $NR^{10}R^{10}$, $NR^{10}R^{11}$, $COOR^{10}$, NO_2, CN, $C(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $C(O)NR^{10}R^{10}$, $N(R^{10})C(O)R^{10}$, $N(R^{10})(COOR^{10})$, $S(O)_nNR^{10}R^{10}$; R^{10}; or C2-C10 alkenyl substituted with 1-3 independent R^9, halo, CF_3, OR^{10}, SR^{10}, $OC(O)R^{10}$, $NR^{11}R^{11}$, $NR^{10}R^{10}$, $NR^{10}R^{11}$, $COOR^{10}$, NO_2, CN, $C(O)R^{10}$, $OC(O)NR^{10}R^{10}$, $C(O)NR^{10}R^{10}$, $N(R^{10})C(O)R^{10}$, $N(R^{10})(COOR^{10})$, $S(O)_nNR^{10}R^{10}$;

Each heterocyclyl is independently a 3-8 membered nonaromatic monocyclic, 8-12 membered nonaromatic bicyclic, or 11-14 membered nonaromatic tricyclic, ring system comprising 1-4 heteroatoms if monocyclic, 1-8 heteroatoms if bicyclic, or 1-10 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S; and

Each heteroaryl is independently a 5-8 membered aromatic monocyclic, 8-12 membered aromatic bicyclic, or 11-14 membered aromatic tricyclic ring system comprising 1-4 heteroatoms if monocyclic, 1-8 heteroatoms if bicyclic, or 1-10 heteroatoms if tricyclic, said heteroatoms independently selected from O, N, or S.

2. The compound of claim 1 wherein,

R^1 is independently R^3; and

R^2 is independently NHR^3.

3. The compound of claim 1 wherein,

R^1 is independently heteroaryl optionally substituted with 1-4 independent R^4 on each ring; and

R^2 is independently NHR^3.

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4. The compound of claim 1 wherein,

R^1 is independently phenyl optionally substituted with 1-5 independent R^4; and

R^2 is independently NHR^3.

5.The compound of claim 1 wherein,

Each R^1 and R^2 is independently NHR^3.

6. The compound of claim 1 wherein,

R^1 is independently NHR^5; and

R^2 is independently NHR^3.

7. The compound of claim 1 wherein,

R^1 is independently NHR^6; and

R^2 is independently NHR^3.

8.The compound of claim 1 wherein,

R^1 is independently OR^5; and

R^2 is independently NHR^3.

9.The compound of claim 1 wherein,

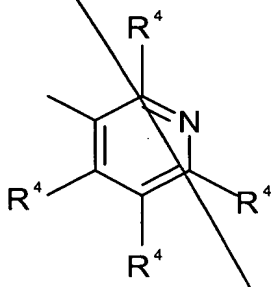
R^1 is independently SR^5; and

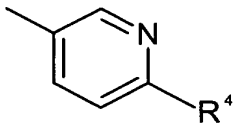
R^2 is independently NHR^3.

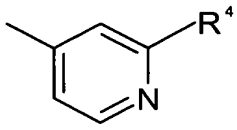
10. The compound of claim 1 wherein:

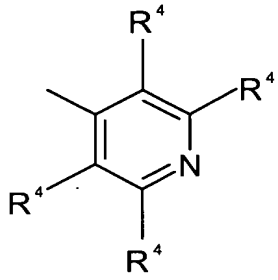
R^2 is independently NHR^3 ; and

R^1 is one of the following groups:









11. The compound of claim 1 wherein,

R^1 is independently heterocyclyl optionally substituted with 1-4 independent R^4 on each ring, wherein said heterocyclyl is not unsubstituted piperidine; and

R^2 is independently NHR^3.

12. The compound of claim 1 wherein,

Each R^1 is independently heteroaryl substituted with 1- 4 independent R^4 on each ring, wherein said heteroaryl comprises at least one nitrogen heteroatom and said heteroaryl is attached at said nitrogen heteroatom; and

Each R^2 is independently NHR^3.

13. The compound of claim 1 wherein,

Each R^1 is independently heterocyclyl substituted with 1- 4 independent R^4 on each ring, wherein said heterocyclyl is not unsubstituted piperidine, and said

heterocyclyl comprises at least one nitrogen heteroatom and said heterocyclyl is attached at said nitrogen heteroatom; and

Each R^2 is independently NHR^3.

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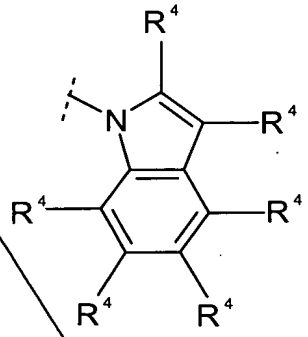
14. The compound of claim 1 wherein,

Each R^2 is independently NHR^3; and

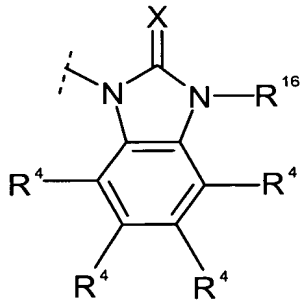
Each R^1 is independently of the formula:



15. The compound of claim 1 wherein,

Each R^2 is independently NHR^3; and

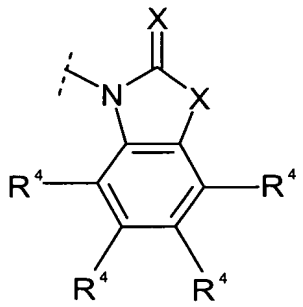
Each R^1 is independently of the formula:



16. The compound of claim 1 wherein,

Each R^2 is independently NHR^3; and

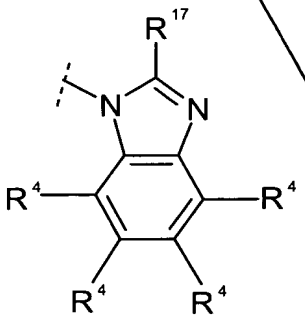
Each R^1 is independently of the formula:



17. The compound of claim 1 wherein,

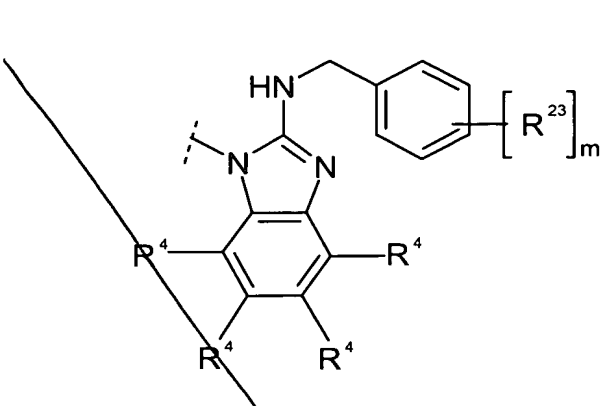
Each R^2 is independently NHR^3; and

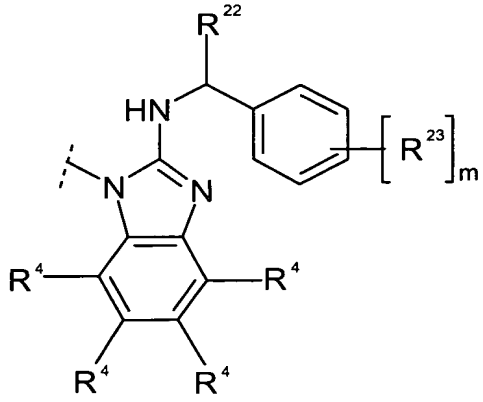
Each R^1 is independently of the formula:



18. The compound of claim 1 wherein,

Each R^1 is independently one of the following groups:

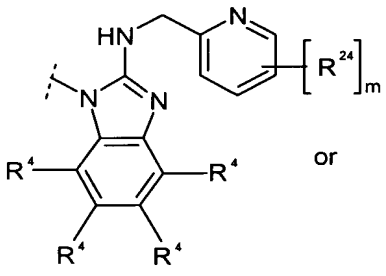




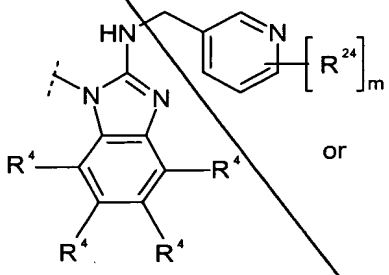
wherein m is 0, 1, 2, 3 or 4.

19. The compound of claim 1 wherein,

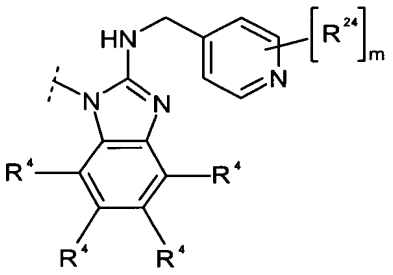
Each R^1 is independently

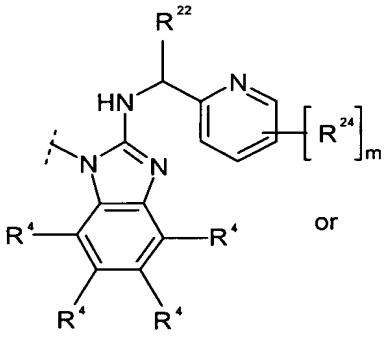


or



or





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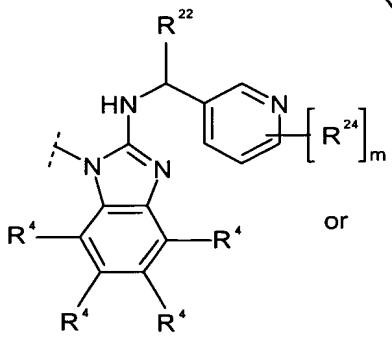

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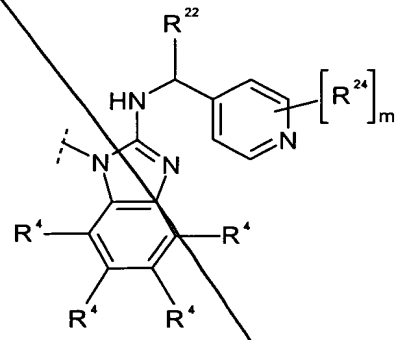
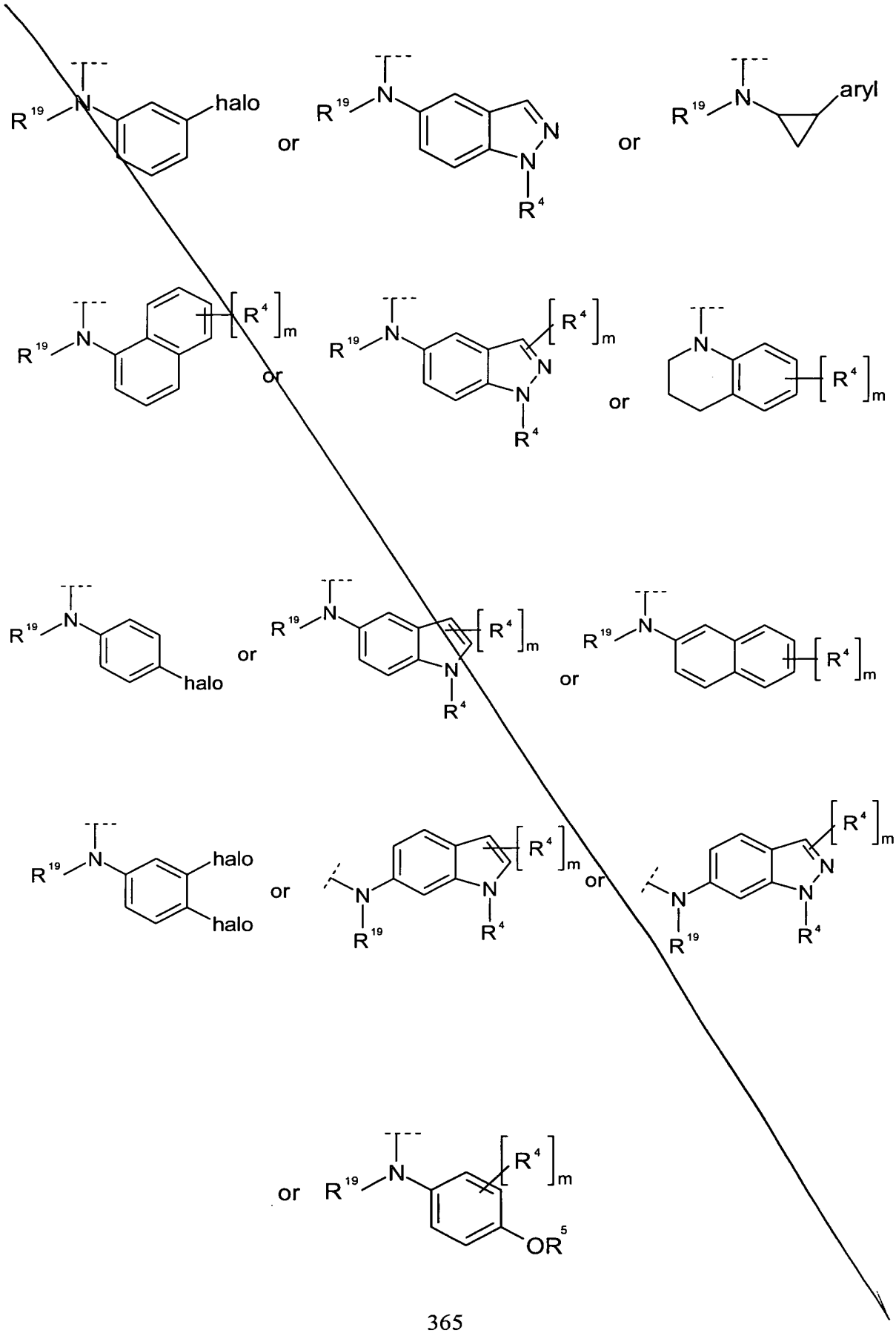


wherein m is 0, 1, 2, 3 or 4.

20. The compound of claim 1 wherein,

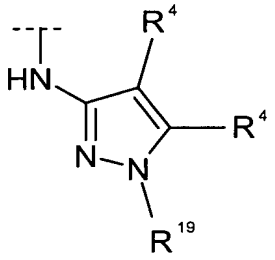
Each R^1 is independently one of the following:



wherein the groups are as defined in claim 1.

21. The compound of claim 1 wherein,

Each R^1 is independently



wherein R^{19} is independently H or C1-C6 alkyl.

22. A composition comprising a compound of any of claims 1-21 and a pharmaceutically acceptable carrier.

23. The composition of claim 22, further comprising at least one additional therapeutic agent.

24. A method of treating kinase-mediated disease or disease symptoms in a mammal comprising administration of a composition comprising a compound of any of claims 1-21.

25. A method of inhibiting kinase activity in a mammal comprising administration of a composition comprising a compound of any of claims 1-21.

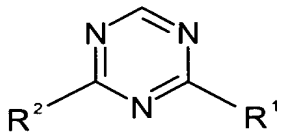
26. A method of treating disease or disease symptoms in a mammal comprising administration of a composition comprising a compound of any of claims 1-21.

27. A method of inhibiting angiogenesis or vasculogenesis activity in a mammal comprising administration of a composition comprising a compound of any of claims 1-21.

28. A method of making a pharmaceutically useful composition comprising combining a compound of any of claims 1-21 with one or more pharmaceutically acceptable carriers.

29. The method of claim 28, further comprising combining an additional therapeutic agent.

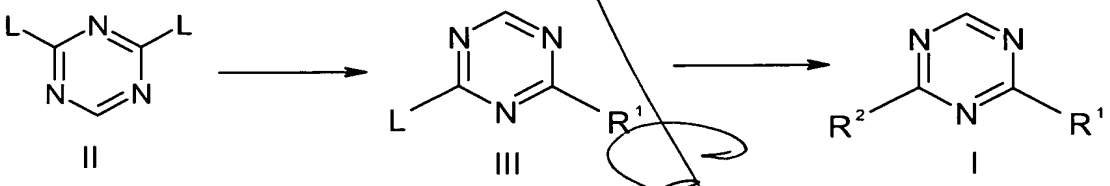
30. A method of making a compound of claim 1 of the formula



wherein

Each R^1 and R^2 is independently R^3; R^8; NHR^3; NHR^5; NHR^6; NR^5R^5; NR^5R^6; SR^5; SR^6; SR^3; OR^5; OR^6; OR^3; $C(O)R^3$; heterocyclyl optionally substituted with 1-4 independent R^4 on each ring; or C1-C10 alkyl substituted with 1-4 independent R^4;

Each R^3 is independently aryl; phenyl optionally substituted with 1-5 independent R^4 on each ring; or heteroaryl optionally substituted with 1-4 independent R^4 on each ring; comprising the steps of :

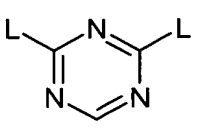
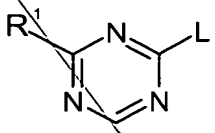
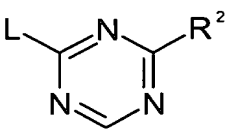


II III I

a) reacting a compound of formula (II) wherein each L is independently a leaving group as defined herein, with a nucleophile of formula H-R^1 (or salt thereof) to give a compound of formula (III); and

b) reacting the compound of formula (III) with a nucleophile of formula $H\text{-}R^2$ (or salt thereof) to give a compound of formula (I).

31. A method of making a compound of claim 1 comprising reacting a triazine of one or more of the formulae:

with an appropriate nucleophilic agent or agents, wherein L is a leaving group and the other groups in said formulae are as defined in claim 1.